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June 14, 2004

Docket # 2004Q-0151 Solae Company Health Claim re Cancer

Dear Ms. Anderson:

Please consider the attached information as you evaluate the petition filed by the Solae Company regarding a health claim for soy-protein-containing products and a reduced risk of certain cancers.

The petitioner Solae contends that its data is "based on the totality of publicly available scientific evidence" when, in fact, their evidence represents a very small portion of the available published studies. We find that the petitioners were highly selective in their choice of evidence and in their commentary, omitting many studies that show soy to be ineffective as a cancer prevention agent, emphasizing favorable outcomes in studies where results were mixed, and providing excuses for results of the few unfavorable studies that they included to give the illusion of balance. Solae states that "to the best of the knowledge of the undersigned, this petition is a representative and balanced submission" although it omitted all mention of the many well-designed studies that have suggested that soy protein can contribute to, cause and accelerate the growth of cancer.

The petitioner Solae contends that their data "establish that there is scientific agreement among experts qualified by scientific training and experience to evaluate such claims regarding the relationship between soy protein products and a reduced risk of certain cancers." In fact, no such consensus exists, and numerous experts qualified by scientific training and experience -- including scientists from the FDA's own National Laboratory for Toxicological Research -- have warned of soy protein's carcinogenic potential and of the health dangers of excess soy-food consumption. We are further concerned because

the petitioner fails to consider soy protein's well-documented risks to the digestive, immune and neuroendocrine systems of the body as well as its high allergenicity.

We have attached a response to Solae's petition to this letter for your consideration. We have included an extended commentary, summaries of important journal articles, quotations from qualified researchers and complete references to publicly available studies, all of which raise questions about or disprove the validity of the proposed health claim.

We maintain that the benefits cited by Solae are putative, not proven, and that longstanding concerns in the scientific community about soy's possible role in carcinogenesis need to be addressed. In the interest of public safety, we therefore request that the Solae petition be declined and the health claim be denied.

Sincerely,

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A. PRELIMINARY REQUIREMENTS

A 1 Solae provides basic information about the amount of soy protein in various soyfoods and states that "soy products contain other nutrients such as carbohydrates, vitamins and minerals, as well as naturally occurring constituents such as fibers, isoflavones and saponins." It neglects to mention here that isoflavones are listed as "carcinogens" in the American Chemical Society's 1976 textbook *Chemical Carcinogens* as well as other toxicology textbooks and that saponins have traditionally been considered antinutrients.

Solae also does not mention that soy protein contains many other constituents that have traditionally been considered antinutrients or toxins. These include protease inhibitors (most notably trypsin inhibitors), phytates, lectins, oxalates and oligosaccharides, which may possess valuable pharmaceutical properties but which have also been linked in more than 100 studies to digestive distress, intestinal disorders, mineral deficiencies, flatulence and even cancer development and growth.

Finally, Solae fails to note that genetically modified soybeans have not been proven to be "substantially equivalent" to regular soybeans and that safety issues have not been properly addressed. Yet soy foods made with both GM and regular soybeans would be eligible for the proposed health claim.

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In its discussion of types of soy foods, Solae states: 'Historically soybean curd and soymilk have been viewed as "traditional" Asian foods. This is only partially true. While tofu dates back to 164 BC, soy milk has a much more recent history in Asia. The earliest historical reference to soy milk as a beverage appears in 1866. *Chinese Medical Journal* articles from the 1930s report that soy milk was not traditional but had become popular as an occasional drink served to the elderly by the 1920s and 1930s. Dr. Harry Miller, an American–born Seventh Day Adventist physician and missionary, was the person in China to invent a commercially feasible method to manufacture soy milk. Dr.

Miller also found out that soy milk was not traditional in Japan and in 1959 wrote an article for *Soybean Digest* entitled "Why Japan Needs Soy Milk." Furthermore, soy milks in today's marketplace bear little relationship to those made in Asia, for they are often made with soy protein isolate and other non-traditional ingredients.

SOURCES

Shurtleff, William. Chronology of soymilk worldwide: Part 1, 220AD to 1949. Special Exhibit, Museum of Soy, 2001. Soyfoods Center, Lafayette, CA.

Guy RA. The diets of nursing mothers and young children in Peiping. *Chinese Med J,* 1936, 50, 434-442.

Guy RA, Yeh KS. Soybean 'milk' as a food for young infants. *Chinese Med J,* 1938, 54, 1, 1-30.

Miller HW, Wen CJ. Experimental studies of soymilk in human nutrition. *Chinese Med J,* 1936, 50, 4, 450-459.

Miller Harry W. Why Japan needs soymilk. *Soybean Digest*, April 1959, 16-17.

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Although Solae claims that soy protein is "safe and lawful," it concedes that soy protein isolate has never actually received GRAS (Generally Recognized as Safe) status as an additive to food. Soy protein was rejected for such status as late as 1999 when a petition submitted by Archer Daniel s Midland for GRAS status for soy protein was returned by CFSAN because of a failure to properly report adverse effects. The petitioner also fails to note that unlike most GRAS substances in use prior to 1958, soy protein isolate was not originally developed as a food but as an industrial product to bind and seal paper products. It therefore does not qualify as a product having a long history of safe use in the food supply. More seriously, soy protein isolate is known to include a number of toxins and carcinogens introduced by the high temperatures, high pressures and chemicals used in its manufacture. In 1979, the Select Committee of GRAS Substances (SCOGS) examined safety issues pertaining to the manufacture of soy protein isolate and recommended that acceptable levels of the carcinogens nitrite and nitrosamines and the toxic amino acid lysinoalanine be established "to avoid future problems." To this date, safe levels have never been established and levels of these substances in edible food products are not closely monitored. The SCOGS committee determined that 150 mg per day of soy protein was the

maximum safe dose, an amount far less than the 4.48 grams that is likely to be consumed by the average American should Solae succeed in obtaining a soy protein and cancer health claim. Solae claims that such "intakes are reasonable and present no safety concerns."

SOURCES

Evaluation of the Health Aspects of Soy Protein Isolates as Food Ingredients. Prepared by Life Sciences Research Office, Federation of American Societies for Experimental Biology for the Bureau of Foods, Food and Drug Administration, 1979. Contract # FDA 223-75-2004.

Sheehan DM, Doerge DR. Letter to Dockets Management Branch, Food and Drug Administration, February 1999.

The SCOGS committee's recommendation of 150 mg of soy protein isolate per day as a "safe dose" is far lower than Solae's estimate of per capita consumption We maintain that soy protein at the higher intake levels projected by Solae would present serious safety concerns, with the biggest risk to people who are allergic to soy.

Soy is widely acknowledged as one of the top eight allergens, with one prominent researcher putting soy in the "top six" and another in the "top four." The increased soy protein in the food supply would not only be found in well-known soyfoods such as tofu, soy milk and veggie burgers – foods that allergy sufferers know enough to avoid -- but also from soy proteins incorporated into the recipes for baked goods, canned, packaged and other processed foods. This "hidden" soy poses a danger to allergy sufferers, who may experience symptoms that range from mild to life threatening, involving, the gastrointestinal, cutaneous and respiratory systems. A recent Swedish study reported four fatalities as the result of soy protein hidden in foods such as hamburgers. Furthermore, allergy experts have warned that the increased use of soy protein in food products is increasing the potential for sensitization.

SOURCES:

FAO Food Allergies Report of the Technical Consultation of the Food and Agricultural Organization of the United Nations, Rome, November 13-14, 1995.

Besler, Matthias Allergen Data Collection: Soybean (Glycine max), *Internet Symposium on Food Allergens* 1999, 1, 2, 51-79. www.food-allergens.de

Bousquet J, Bjorksten B et al. Scientific criteria and selection of allergenic foods for labeling. *Allergy*, 1998, 53 (Suppl 47) 3-21.

Burks AW, Brooks JR, Sampson HA. Allergenicity of major component proteins of soybean determined by enzyme-linked immunosorbent assay (ELISA) and immunoblotting in children with atopic dermatitis and positive soy challenges. *J Allergy Clin Immunol*, 1988, 81, 1135-1142.

Burks AW, Williams LW et al. Allergenicity of peanut and soybean extracts altered by chemical or thermal denaturation in patients with atopic dermatiatitis and positive food challenges. *J. Allergy Clin Immunol*, 1992, 90 (6 pt 1), 889-897.

Sampson HA, McCaskill CM. Food hypersensitivity and atopic dermatitis: evaluation of 113 pateints. J Ped. 1985, 107, 669. Documented soy protein to be one of the major food antigens, wich incluedes milk, peanut, wheat, egg and fish.

Foucard T, Malmheden-Yman I. A study on severe food reactions in Sweden – is soy protein an underestimated cause of food anaphylaxis. *Allergy*, 1999, 53, 3, 261-265.

We are also concerned that a claim that soy protein reduces cancer would encourage many health conscious consumers to eat far more soy protein than Solae's projected average of 4.48 g per day. People at special risk are vegetarians and vegans who choose soy as their main source of protein, individuals trying to prevent or reverse cancer and other diseases, and those at risk for or afflicted with thyroid disease. The Working Group of the British Committee on Toxicology (COT) recently "identified individuals with hypothyroidism as a subgroup of potential concern," noting that a "soy-rich diet may provide sufficient concentrations of phytoestrogens to interfere with thyroxine replacement therapy." Daniel Sheehan, Ph.D. and Daniel Doerge, Ph.D, of the FDA's National Laboratory of Toxicological Research in Arkansas, have warned that "Isoflavones are inhibitors of thyroid peroxidase, which makes T3 and T4. Inhibition can be expected to generate thyroid abnormalities, including goiter and autoimmune thyroiditis. There exists a significant body of animal data that demonstrates goitrogenic and even carcinogenic effects of soy products."

Solae has also not addressed the likelihood that increased genistein in the food supply as a result of increased soy intake would have a cumultative or exponential effect with other xenoestrogens in the environment. Toxicologists at the Centre for Toxicology, The School of Pharmacology at the University of London have stated that "estrogenic agents are able to act together to produce significant effects when combined at

concentrations below their NOECs. . . Hazard assessments that ignore the possibility of joint action of estrogenic chemicals will almost certainly lead to significant underestimations of risk.

Later in this document, we will present a substantial number of studies showing that soy can contribute to, cause and/or accelerate the growth of cancer. Given the number of such studies and the strong warnings of respected scientists, including the FDA's own Drs Sheehan and Doerge, we find it highly disturbing that Solae would put its commercial interests above public health and propose a cancer prevention health claim for soy protein.

SOURCES:

Committee on Toxicology (UK) Draft Report on Phytoestrogens.
http://www.foodstandards.gov.uk/multimedia/webpage/phytoreportworddocs

Silva E, Rajapakse N, Kortenkamp A. Something from "nothing' – eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. *Environ Sc Technol*, 2002, 36, 8, 1751-1756.

Sheehan DM, Doerge DR. Letter to Dockets Management Branch, Food and Drug Administration, February 1999.

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Solae notes geographical differences in cancer morbidity and mortality, and includes the striking fact that the death rate from breast cancer is 4-fold lower and from prostate cancer 18-fold lower in China than in the United States. While soy may be a factor in these reduced rates, other dietary and lifestyle factors are almost certainly involved. Certainly, there is no direct evidence for beneficial cancer–reducing effects of the phytoestrogens in soy protein foods. More importantly, we contend that if the petitioners attributes decreased rates of breast, prostate and colon cancer in Asia to soy consumption, then the same logic would require them to blame higher rates of cancer of

the esophagus, stomach, thyroid, pancreas and liver in Asian countries on consumption of soy. They have not done so.

Solae has also neglected to inform the FDA's examiners that proper use of soy protein for cancer prevention requires sure knowledge of windows of vulnerability – or opportunity – as found in utero, during infancy, before puberty, during puberty, the reproductive years and beyond. Ratther, this company proposes an indiscriminate increase in consumption of soy protein for men, women and children with no admission of the fact that a substance that might be helpful in one stage of the life cycle could be harmful in another. Research to date is inconsistent and contradictory, but leaves no doubt that the phytoestrogens in soy protein exert their influence throughout the body in many different ways and that they have the potential to exert adverse as well as beneficial actions. Patricia L Whitten PhD of Emory University explains that "these potential roles fall into three major areas: 1) estrogen agonists whose activational actions could prove beneficial to postmenopausal women but might be harmful to the degree that they contribute to carcinogenesis or other adverse effects. 2) antiestrogens or antiproliferative agents that could help to prevent estrogen-dependent carcinoma by antagonizing estrogen action but could also contribute to infertility by suppressing normal reproductive function and 3) developmental toxins that could disrupt sexual differentiation by altering sex-specific patterns of development but might also provide protection against environmental estrogens by altering steroid response thresholds." We believe that it is irresponsible of Solae to claim possible benefits of soy protein without warning consumers of possible risks.

SOURCE

Whitten PL, Lewis C et al. Potential Adverse Effects of phytoestrogens. *J Nutr*, 1995, 125, 771S-776S.

B. SCIENTIFIC EVIDENCE

B1

Solae states that "soy protein is a major source of dietary protein worldwide." It is certainly true that soy protein consumption has been increasing worldwide, but the claim that soy constitutes a "major source of dietary protein" is inaccurate. In any case, high levels of soy consumption is a recent phenomenon, the result of intense marketing efforts by the soy industry and/or giveaways by government and charitable organizations.

Soy foods have been a dietary component in some Asian countries for centuries, not millennia, and are eaten there in small amounts as a condiment, not as a staple. Furthermore, the types of soy foods eaten traditionally in the countries of Asia are almost entirely whole soy foods prepared by fermentation and precipitation methods, not fractionated soy proteins produced by industrial food processing. This difference is highly significant in that modern processing methods used by the soy industry produce nitrosamines and other carcinogens. A recent study from the University of Illinois at Urbana-Champaign indicates that "highly processed soy may stimulate estrogen-dependent breast cancer." According to Dr. Willliam Helferich, one of the study's authors, "Soy has been correlated with low rates of breast cancer in Asian populations, but soy foods in Asia are made from minimally processed soybeans or defatted, toasted soy flour, which is quite different from soy products consumed in the U.S." We include this important study later in our section on Breast Cancer.

Solae boldly writes that "the totality of publicly available scientific evidence supports the substance/disease relationship that consumption of soy protein-containing foods is related to a lower risk of certain cancers. The evidence is particularly strong in cancer of breast, prostate and gastrointestinal tract." In fact, we will establish that Solae has not presented "the totality" of publicly available evidence. Nor have scientists reached a consensus regarding soy and cancer. Indeed, many respected researchers believe that the isoflavones in soy protein can contribute to, cause and/or accelerate the growth of cancer.

We also dispute the validity of Solae's claim that meta-analyses prove a positive relationship between soy consumption and cancer risk. Meta-analysts have been criticized by many in the scientific and statistical communities for making faulty assumptions, indulging in creative accounting and for leaving out studies that contradict or dilute the conclusions desired. Solae has left out many such studies.

Finally, the petitioners further assert that animal studies support their cancer claim and state that there are "39 studies available to date." This number represents a fraction of the available studies, a selection that Solae has weighed towards positive findings. Later in this response, we will provide a sampling of the many animal studies that suggest soy's ineffectiveness as a chemoprotective agent and its possible role in carcinogenesis.

B3

B3 1 BREAST CANCER

This section of Solae's petition "considers the weight of scientific evidence that relates dietary soy protein to the risk of breast cancer in women" and concludes that "the totality of the publicly available scientific evidence supports the substance/disease relationship that consumption of soy protein-containing foods is associated with a lower risk of breast cancer in women."

More accurately, this section presents scientific evidence suggesting that soy protein is protective. A more comprehensive review of the studies would reveal that the results are both inconsistent and inconclusive. Solae does include several studies that show no effect between soy intake and breast cancer risk but seems to have chosen them because they were easy to dismiss for a variety of reasons. Most seriously, Solae failed to include any studies that would substantially undermine their premise that soy protein reduces breast cancer risk.

Later in this response we will present a number of well-designed studies that rebut and refute Solae's position that soy is protective against breast cancer. First, we would like to make a few points about some of the studies cited by Solae.

Nagata et al 2000 shows that soy protein intake is not associated with lowered risk of breast cancer, prostate or lung cancer in Japanese people. Soy protein was associated with a lowered risk of stomach cancer but also with a higher risk of death from colorectal cancer. To its credit, Solae did not omit either this study or this information. The results, however, must not be minimized. This large-scale ecological study resulted in statistically valid conclusions and provides strong evidence of risk colorectal cancer from soy protein consumption. We do not feel it is ethical to dismiss the validity of this study by rolling it into a meta-analysis of all soy-and-cancer prevention studies.

Key et al 1999, a large prospective study of 34, 759 women in Japan, found no significant association between breast cancer risk and consumption of soy foods. Solae dismisses this study because it was carried out in Hiroshima and Nagasaki, cities where women were exposed to high levels of ionizing radiation because of the atomic bomb. The fact that women consuming high levels of soy protein did not enjoy special protection, however, is very significant. Proponents of soy foods often claim that soy foods provide protection against the growing numbers of carcinogens in the environment. The findings of Key et al prove otherwise, and match the results of animal research in which cancer was induced but soy-protein diets failed to confer protection.

Ingram et al 1997 show that high excretion of both equol and enterolactone were associated with a lowering of breast-cancer risk. There were no associations with the parent phytoestrogens daidzein and matairesinol. This suggests that metabolism of these compounds by the gut microflora may be vitally important. If so, soy protein intake alone would not be the most relevant factor in the lowering breast cancer risk. In several studies Setchell and colleagues have found that some women are equol producers and others are not. Given the fact that equol production can be considered a marker of gastrointestinal health, this study might support the role of a healthy gut in cancer prevention. Recent studies – most notably *Journal of the American Medical Association* (February 18, 2004; 291(7):827-35)—have linked levels of breast cancer risk to levels of

antibiotic usage. Antibiotics can affect bacteria in the intestine, which may impact the ways in which foods that might prevent cancer are broken down in the body. Antibiotics may also affect the body's immune response and response to inflammation, which could also be related to the development of cancer Women with frequent infections treated by antibiotics may also be generally less healthy as those without such infections, and may therefore be more prone to the development of breast cancer. The accompanying *JAMA* editorial noted that the finding is particularly worrisome as exposure to antibiotics is so prevalent, and often not necessary. *JAMA*'s editors raised the question of whether the use of antibiotics is a risk factor for other cancers, and point to a need for further research to address this concern.

Yuan et al 1995. The researchers state their conclusion very clearly. "Our study does not support the hypothesis that high intake of soy protein protects against breast cancer." Women living in Shanghai and Tianjin consumed 3.5 g/d and 2.8g/d, respectively, levels that are approximately one-third of the average intake reported in the Shanghai Breast Cancer Study (Dai et al 2001, Shu et al 2001). Solae comments: "It is likely that the intake is underestimated in the Yuan study as the study is not specifically designed to evaluate the effect of soyfoods and soy intake ascertainment is incomplete." In fact, many researchers have found that soy intake in many parts of China is lower than that given in soy industry figures. Accordingly, factors other than soy need to be looked at in connection with China's low breast cancer rate.

Yamamoto et al 2003. Solae points out the lack of significant relationship between soyfoods and breast cancer here might be due to a small number of breast cancer cases. The authors of the study state, "possible associations between breast cancer risk and soyfoods that were not statistically significant in our study may be detected among larger sample sizes." This is speculation, and cannot properly be used in defense of a soy protein/cancer reduction health claim.

Wu et al 1996 indicate that the risk of breast cancer decreases significantly with increased tofu intake, but that there is a lack of statistical significance in postmenopausal

women. Solae comments: "This appears to be solely an effect of the larger number of premenopausal than postmenopausal women since the magnitudes of effects are very similar." However, the researchers found "the association was only significant in women born in Asia and not among women of Asian origin born in the US," suggesting the presence of other dietary and lifestyle factors.

Hakkak R, Korourian S et al. Solae notes that "feeding rats a diet containing 20% ISP for two generations significantly decreases tumor incidence and increases tumor latency period in F2 offspring compared with the controls fed a casein-based diet." The study, however, indicates that both whey and SPI caused a reduction in tumour number and increased tumour latency in both the F1 and F2 generations compared to controls. Animals receiving whey exhibited a reduction in tumour incidence but only animals in the subsequent generation fed SPI had a reduced tumour incidence.

Solae also omits mention of Hakkak's finding of a 1-day advance in vaginal opening observed in the animals fed soy protein isolate compared to those fed whey or control. This is evidence of premature sexual maturation and suggests that increased soy in the food supply could put young girls at increased risk for precocious puberty, itself a well-known risk factor for breast cancer.

den Tonkelaar I, Keinan-Boker L et al. Solae states "A high urinary genistein is associated with a lower risk breast cancer in this study population, although results are not statistically significant." The researchers conclusion is more definitive. "We were not able to detect the previously reported protective effects of genistein and enterolactone on breast cancer risk in our postmenopausal population of Dutch women. Such an effect may be smaller than expected and/or limited to specific subgroups of the population."

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We could raise many other questions about the validity of the results of the studies chosen by Solae, but the most damaging evidence is found in studies that Solae

chose to exclude. We would like to draw attention to a group of studies showing that soy protein causes the proliferation of breast cancer cells. This not only increases a woman's risk of developing breast cancer but poses special dangers to people already afflicted with breast cancer. The latter group includes not only women who have already been diagnosed with breast cancer, but those in the early stages prior to diagnosis.

We are not alone in this concern. The British government's Committee on Toxicology (COT) writes in Chapter 15 -- Phytoestrogens and Cancer of its "Working Draft on Phytoestrogen" that "Short term dietary supplementation has been shown to cause a proliferative response in premenopausal women with breast disease whereas a proliferative effect was not reported in premenopausal women without breast disease. However, phytoestrogen treatment did induce a weak estrogenic effect in these women as shown by modulation of the levels of the oestrogen responsive gene products apolipoprotein D and pS2 in nipple aspirate."

COT further states: "The animal data on breast cancer is conflicting. A number of studies have shown that genistein has a protective effect in animal models of chemically induced cancer. However, similar experiments using tumour implant models showed that genistein stimulated the growth of implanted mammary tumours both by dietary and subcutaneous administration." The full text of this report can be found at http://www.foodstandards.gov.uk/multimedia/webpage/phytoreportworddocs

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The following studies establish that soy protein (and its constituent isoflavones) have the potential to increase breast cancer risk and disease progression. All quotations included are from the original journal articles.

Dees C, Foster JS et al. Dietary estrogens stimulate human breast cells to enter the cell cycle. *Environ Health Perspect*, 1997, 105, 633-636.

"Genistein, a dietary estrogen, inhibits the growth of breast cancer cells at low doses but additional studies have suggested that genistein stimulates proliferation of breast cancer cells. . . Our findings are consistent with a conclusion that dietary estrogens

do not act as anti-estrogens, but act like DDT and estradiol to stimulate breast cancer cells to enter the cell cycle. Women should not consume particular foods (soy derived products) to prevent breast cancer."

Martin PM, Horwitz KB et al. Phytoestrogen interaction with estrogen receptos in human breast cancer cells. *Endocrinol,* 1978, 103, 5, 1860-1867**.**

"The interactions of phytoestrogens with estrogen receptors were studied in the human breast cancer cell line, MCF-7. The phytoestrogens are also biologically active; they can markedly enhance tumor cell proliferation. In sum, phytoestrogens interact with the estrogen receptors of human breast cancer cells in culture and, therefore, may affect estrogen-mediated events in these cells."

Allred CD, Ju YH et al. Dietary genistein stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein. *Carcinogenesis,* 2001b, 22, 1667-1673.

"The estrogenic soy isoflavone, genistein, stimulates growth of estrogen-dependent human breast cancer (MCF-7) cells in vivo. Dietary genistein resulted in increased tumor growth, pS2 expression and cellular proliferation similar to that observed with genistein. The remaining mice were switched to diets free of genistein and genistein. When mice were placed on isoflavone-free diets, tumors regressed over a span of 9 weeks, metabolism of genistein to genistein occurred. .. . In summary, the glycoside genistein, like the aglycone genistein, can stimulate estrogen-dependent breast cancer cell growth in vivo. Removal of genistein or genistein from the diet caused tumors to regress."

Allred CD, Allred KF, et al. Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (MCF-7) tumors in a dose dependent manner. *Cancer Res,* 2001, 61, 13, 5045-5050.

"We have demonstrated that genistein stimulates growth of estrogen-dependent human breast cancer (MCF-7) cells in vivo (C.Y. Hsieh et al, Cancer Res, 58, 3833-3838, 1998). The isoflavones are a group of phytoestrogens that are present in high concentrations in soy. Soy protein dits containing varying amounts of genistein

increased estrogen-dependent tumor growth in a dose dependent manner . . . Cell proliferation was greatest in tumors of animals given estrogen or dietary genistein (150 and 300 ppm). . . Here we present new information that soy protein isolates containing increasing concentrations of genistein stimulate the growth of estrogen-dependent breast cancer cells in vivo in a dose-dependent manner.

Allred CD, Allred KF et al. Dietary genistein results in larger MNU-induced, estrogen dependent mammary tumors following ovariectomy of Sprague-Dawley rats. Carcinogenesis, 2004, 25, 2, 211-218.

"The data suggest that in an endogenous estrogen environment similar to that of a postmenopausal woman, dietary genistein can stimulate the growth of a mammary carcinogen MNU-induced estrogen-dependent mammary tumours."

Allred CD, Allred KF et al. Soy processing influences growth of estrogen-dependent breast cancer tumors in mice. *Carcinogenesis,* May 6, 2004.

"Soy-based products consumed in Asian countries are minimally processed whereas in the U.S. many of the soy foods and soy ingredients are highly processed. Soy foods contain complex mixtures of bioactive compounds which may interact with one another. The objective of this study was to evaluate the ability of various soy products containing genistein, the glycoside form of genistein to affect growth of MCF-7 cells transplanted into ovariectomized athymic mice. . . . Tumors in the negative control animals regressed throughout the study while tumors in the soy flour-fed animals remained basically the same size (neither grew nor regressed). In animals consuming soy molasses, Novasoy ®, mixed isoflavones or genistein alone tumor growth was stimulated when compared to animals consuming a control diet devoid of soy. These same dietary treatments resulted in increased cellular proliferation."

Hsich CY, Santell RC, et al. Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells in vitro and in vivo. *Cancer Res,* 1998, 58, 3833-3838.

"Genistein, found in soy products, is a phytochemical with several biological activities. In the current study, our research focused on the estrogenic and proliferation-inducing activity of genistein. We have demonstrated that genistein enhanced the proliferation of estrogen-dependent human breast cancer (MCF-7) cells in vitro at concentrations as low as 10nM, with a concentration of 100nM achieving proliferative effects similar to those of 1 nM estradiol."

Ju YH, Doerge DR et al. Dietary genistein negates the inhibitory effects of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. *Cancer Res,* 2002, 1, 62, 9, 2474-2477.

"We investigated interactions between the soy isoflavone, genistein, and an antiestorgen, tamoxifen (TAM), on the growth of estrogen (E)-dependent breast cancer (MCF-7) cells. Dietary genistein negated/overwhelmed the inhibitory effect of TAM on MCF-7 tumor growth, lowered E2 level in plasma and increased expression of E-resonsive genes (.e.g. pS2, PR, and cyclin D1). Therefore caution is warranted for postmenopausal women consuming dietary genistein while on TAM therapy for E-responsive breast cancer."

McMichael -Phillips DF, Harding C et al. Effects of soy-protein supplementation on epithelial proliferation in the histologically normal human breast. *Am J Clin Nutr,* 1998, 68 (6 Suppl), 1431S-1435S.

This study examines the effects of dietary soy supplementation on the proliferation rate of premenopausal histologically normal breast epithelium and the expression of progesterone receptor. The proliferation rate of breast lobular epithelium significantly increased after 14d of soy supplementation when both the day of menstrual cycle and the age of patient were accounted for. . . Short-term dietary soy stimulates breast proliferation; further studies are required to determine whether this due to estrogen agonist activity and to examine the long-term effects of soy supplementation on the pituitary gland and breast."

de Lemos ML. Effects of soy phytoestrogens genistein and daidzein on breast cancer growth. *Ann Pharmacother*, 2001, 35, 9, 1118-1121.

"OBJECTIVE: To determine whether genistein and daidzein, the major phytoestrogens in soy, can stimulate breast cancer growth. . . . CONCLUSIONS: Genistein and daidzein may stimulate existing breast tumor growth and antagonize the effects of tamoxifen. Women with current or past breast cancer should be aware of the risks of potential tumor growth when taking soy products."

Wang C, Kurzer MS. Phytoestrogen concentration determines effects on DNA synthesis in human breast cancer cells. Nutr Cancer, 1997, 28, 3, 236-247.

"Our data suggest the possibility that, at typical concentrations in humans, phytoestrogens and related flavonoids and lignans may stimulate, rather than inhibit, growth of estrogen-dependent tumours. . . In conclusion, most of the phytoestrogens and related compounds tested in this study showed stimulation of DNA synthesis in estrogen-dependent MCF-7 cells at low concentrations and inhibition of DNA synthesis in MCF-7 and estrogen-independent MDA-MB-231 cells at high concentrations. Although we observed inhibition at high levels, it is extremely important to consider that, at concentrations close to probable levels in humans, DNA synthesis was significantly induced in MCF-7 cells."

Ju YH, Allred CD et al. Physiological concentrations of dietary genistein dose-dependently stimulate growth of estrogen-dependent human breast cancer (MCF-7) tumors implanted in athymic nude mice. *J Nutr*, 2001, 131, 11, 2957-2962.

"In conclusion, dietary treatment with genistein at physiological concentrations produces blood levels of genistein sufficient to stimulate estrogenic effects, as breast tumor growth, cellular proliferation and pS2 expression in athymic mice in a dose-resonsive manner similar to that seen in vitro."

* * * * *

Phytoestrogens such as genistein found in soy protein products can cross the placenta, putting unborn children at risk. We present here two studies that show that perinatal exposure could increase the risk of babies developing breast cancer.

Hilakivi-Clark L, Cho E, Clark R. Maternal exposure to genistein during pregnancy increases carcinogen-induced mammary tumorigenesis in female rat offspring. *Oncol Rep,* 1998, 5, 609-616.

"Human and animal data indicate that a high maternal estrogen exposure during pregnancy increases breast cancer risk among daughters. This may reflect an increase in the epithelial structures that are the sites for malignant transformation, i.e. terminal end buds (TEBs), and a reduction in epithelial differentiation in the mammary gland. Some phytoestrogens, such as genistein, which is a major component in soy-based foods, ... have estrogenic effects on the reproductive system, breast and brain. .. These findings indicate that maternal exposure to physiological doses of genistein mimics the effects of E2 on the mammary gland and reproductive systems in the offspring. Thus our results suggest that genistein acts as an estrogen in utero, and may increase the incidence of mammary tumors if given through a pregnant mother. "

Yang J, Nakagama H et al. Influence of perinatal genistein exposure on the development of MNU-induced mammary carcinoma in female Sprague-Dawley rats. Cancer Lett, 2000, 149 (1-2), 171-179.

"Perinatal genistein is an endocrine disrupter and increases multiplicity of MNU-induced mammary carcinoma in rats."

* * * * *

Women are at greater risk for breast cancer if they have abnormal cytology in nipple aspirates of breast fluid. (Wrensch MR, Petrakis NL et al. Breast cancer risk in women with abnormal cytology in nipple aspirates of breast fluid. *J Natl Cancer Inst,* 2001, 5, 93, 23, 1791-1798.). The following study indicates that soy proteins increase

breast fluid, cause epithelial hyperplasia and contribute to other abnormalities associated with increased risk of breast cancer.

Petrakis NL. Barnes S et al. Stimulatory influence of soy protein isolate on breast cancer secretion in pre-and postmenopausal women. *Cancer Epidemiol Biomarkers Prev*, 1996, 10, 785-794.

"Soy foods have been reported to have protective effects against premenopausal breast cancer in Asian women. No studies have been reported on potential physiological effects of dietary soy consumption on breast gland function. We evaluated the influence of the long-term ingestion of a commercial soy protein isolate on breast secretory activity. We hypothesized that the features of nipple aspirate fluid (NAF) of non-Asian women would be altered so as to resemble those previously found in Asian women. . . . Of potential concern was the cytological detection of epithelial hyperplasia in 7 of 24 women (29.2%) during the months they were consuming soy protein isolate. The findings did not support our a prior hypothesis. Instead, this pilot study indicates that prolonged consumption of soy protein isolate has a stimulatory effect on the premenopausal female breast, characterized by increased secretion of breast fluid, the appearance of hyperplastic epithelial cells and elevated levels of plasma estradiol. These findings are suggestive of an estrogenic stimulus from the isoflavones genistein and daidzein contained in soy protein isolate. "

Hargreaves DF, Potten CS et al. Two-week soy supplementation has an estrogenic effect on normal premenopausal breast. *J. Clin Endocrinol Metab,* 1999, 84, 4017-4024.

"Short term dietary soy has a weak estrogenic response on the breast, as easured by nipple aspirate apolipoprotein D and pS2 expression. No antiestrogenic effect of soy on the breast was detected."

* * * * *

B3.2. Prostate Cancer

Solae states that “the totality of the publicly available scientific evidence supports the substance/disease relationship that consumption of soy protein-containing foods is related to a lower risk of prostate cancer in men.” We submit that the British Committee on Toxicity (COT) is correct when it states in its “Working Draft on Phytoestrogens” that “The epidemiological data on soy intake and prostate cancer are inconsistent” and that concentrations used in animal experiments are “very high compared with the likely dietary exposure levels in humans.”
http://www.foodstandards.gov.uk/multimedia/webpage/phytoreportworddocs

Solae seems far more confident about the favorable conclusions in the studies it cites than are the researchers themselves, who often qualify their claims with phrases such as “the findings are not conclusive and require further investigation." Two examples are: “Possible associations between soy bean products, isoflavones and prostate cancer risk should be further investigated.” (Jacobsen, 1998) **“**More research is needed on these dietary factors and the subsequent development of prostate cancer before any firm conclusions can be drawn.” (Severson. 1989)

* * * * *

We contend that many dietary factors may be involved in the reduced rates of prostate cancer in Asia. The following studies indicate that soy consumption is linked to reduced incidences of prostate cancer, but suggest that soy is not the only dietary factor. Green tea, nuts, grains, rice, fish and other foods alone or in combination with or without soy might contribute to the reduced cancer risk. Severson, Kolonel and Hebert are three researchers cited by Solae who help make our case. All quotations in this and other sections are for the words of the researchers.

Severson,K, Nomura AM et al. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res.* 1989, 1, 49, 7, 1857-1860.

"Prostate cancer incidence was prospectively studied among 7999 men of Japanese ancestry who were first examined between 1965 and 1968 and then followed through 1986. During this surveillance period, 174 incident cases of prostate cancer were recorded. Increased consumption of rice and tofu were both associated with a decreased risk of prostate cancer . . . "

Kolonel LN, Hankin JH et al. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. *Cancer Epidemiol Biomarkers Prev.* 2000, 8, 795-804.

"The evidence for a protective effect of vegetables, fruits, and legumes against prostate cancer is weak and inconsistent. We examined the relationship of these food groups and their constituent foods to prostate cancer risk in a multicenter case-control study of African-American, white, Japanese, and Chinese men. Cases (n = 1619) with histologically confirmed prostate cancer were identified through the population-based tumor registries of Hawaii, San Francisco, and Los Angeles in the United States and British Columbia and Ontario in Canada. Controls (n = 1618) were frequency-matched to cases on ethnicity, age, and region of residence of the case, in a ratio of approximately 1:1. Intakes of yellow-orange and cruciferous vegetables were also inversely related to prostate cancer, especially for advanced cases, among whom the highest quintile OR for yellow-orange vegetables = 0.67 (P for trend = 0.01) and the highest quintile OR for cruciferous vegetables = 0.61 (P for trend = 0.006). Intake of tomatoes and of fruits was not related to risk. Findings were generally consistent across ethnic groups. These results suggest that legumes (not limited to soy products) and certain categories of vegetables may protect against prostate cancer."

Hebert JR, Hurley TG et al. Nutritional and socioeconomic factors in relation to prostate cancer mortality: a cross-national study. *Natl Cancer Inst.* 1998, 90, 21, 1637-47.

"CONCLUSIONS: The specific food-related results from this study are consistent with previous information and support the current dietary guidelines and hypothesis that grains, cereals, and nuts are protective against prostate cancer. The findings also provide a rationale for future study of soy products in prostate cancer prevention trials."

Adlercreutz H. Phyto-oestrogens and cancer**.** *Lancet Oncol.* 2002. 3, 6, 364-373.

"Whether these observed protective effects are caused by the presence of dietary phyto-oestrogens, or whether they are merely indicators of a healthy diet in general, has not been established."

Sonoda T, Nagata Y, A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. *Cancer Sci.* 2004, 95, 3, 238-242.

"The age-adjusted incidence of prostate cancer is low in Japan, and it has been suggested that the traditional Japanese diet, which includes many soy products, plays a preventive role against prostate cancer. We performed a case-control study on dietary factors and prostate cancer in order to assess the hypothesis that the traditional Japanese diet reduces the risk of prostate cancer. . . Consumption of fish, all soybean products, tofu (bean curds), and natto (fermented soybeans) was associated with decreased risk. . . . Our results provide support to the hypothesis that the traditional Japanese diet, which is rich in soybean products and fish, might be protective against prostate cancer."

Zhou JR, Yu L, Zhong Y, Blackburn GL. Zhou Soy phytochemicals and tea bioactive components synergistically inhibit androgen-sensitive human prostate tumors in mice, J Nutr. 2003, 133, 2, 516-21.

"Although high doses of single bioactive agents may have potent anticancer effects, the chemopreventive properties of the Asian diet may result from interactions among several components that potentiate the activities of any single constituent. In Asia, where intake of soy products and tea consumption are very high, aggressive prostate cancer is significantly less prevalent in Asian men. The objective of the present study was to identify possible synergistic effects between soy and tea components on prostate tumor progression in a mouse model of orthotopic androgen-sensitive human prostate cancer. . . . The combination of SPC and green tea synergistically inhibited final tumor weight and metastasis and significantly reduced serum concentrations of both testosterone and DHT in vivo. Inhibition of tumor progression was associated with reduced tumor cell proliferation and tumor angiogenesis. This study suggests that further

research is warranted to study the role of soy and tea combination as effective nutritional regimens in prostate cancer prevention."

* * * * *

We would like to bring to your attention the following group of human and animal studies omitted from Solae's "thorough review of the literature." These studies not only show that soy foods are *not* protective against prostate cancer or are less effective than other dietary agents, but also that soy protein – and its constituent isoflavones -- have been linked to *increased* prostate cancer risk. In addition, these dietary compounds have caused undesirable side effects, including changes to the dimorphic brain region and increased IGF-1 levels.

Urban D, Irwin W et al. The effect of isolated soy protein on plasma biomarkers in elderly men with elevated serum prostate specific antigen. *Clin Cancer Res*, 2001, 7, 1782-1789,

This was a randomized, double blind crossover study in which 34 elderly men with elevated PSA received a soy beverage twice daily for six weeks.

"CONCLUSIONS: This study reveals that short-term exposure of elderly men with elevated serum PSA values to soy protein containing isoflavones decreases serum cholesterol but not the serum biomarkers PSA and p105erbB-2."

Adams KF, Chen C et al. Soy isoflavones do not modulate prostate-specific antigen concentrations in older men in a randomized controlled trial. *Cancer Epidemiol biomarkers Prev*, 2004, 13, 4, 644-648.

"Mortality rates for prostate cancer are low in Asia but high in the West. One explanation is the high level of soy consumption in Asia. Soy isoflavones reduce prostate tumor growth in many, but not all, animal models. Elevated levels of serum prostate-specific antigen (PSA) are a marker of prostate tumor growth. Our objective was to

determine whether 12-month soy isoflavone supplementation would alter serum PSA concentrations in healthy, older men. . . . We found no evidence that a 12-month 83 mg/day isoflavone treatment alters serum PSA concentration or velocity in seemingly healthy men aged 50-80 years."

Bylund A, Zhang JX et al. Rye bran and soy protein delay growth and increase apoptosis of human LNCaP prostate adenocarcinoma in nude mice. *Prostate.* 2000, 1, 42, 4, 304-14.

"CONCLUSIONS: Factors in rye bran and soy protein may inhibit prostate cancer growth. The effect is more apparent for rye than for soy. Further studies are needed to identify the effective substances and to explore the mechanism."

Hirayama T. Epidemiology of prostate cancer with special reference to the role of diet. *Natl Cancer Inst Monogr,* 1979, 53, 149-155.

"This was a prospective epidemiologic study of prostate cancer was conducted in Japan. The 10-year follow-up study of 122,261 men aged 40 years and above, who constitute 94.5% of the census population of 29 Health Center Districts, revealed a significantly lower age-standardized death rate for prostate cancer in men who daily ate green and yellow vegetables. This association is consistently observed in each age-group, in each socioeconomic class, and in each prefecture. Selected epidemiologic phenomena, such as the upward trend of the prostate cancer death rate in Japan, intracountry variation of death rate, the significantly lower incidence rate in Japan compared with that of the United States, and elevated risk in Japanese migrants to Hawaii, appear to be explained by the variation in diet and change in amount of green and yellow vegetables ingested. The possible role of vitamin A is considered as a factor in preventing and inhibiting growth of prostate cancer. Most of the other factors studied appear noncontributory, except for marital status; a higher risk was observed in 'ever married' men."
The data from this study indicate a significantly increased risk of prostate cancer associated with the consumption of miso.

Solae states that it chose to exclude studies on miso because it is relatively low in soy protein. However, miso does include soy isoflavones. We therefore believe that the results from this large-scale study are relevant In addition, Dr. Hirayama offers a convincing alternative explanation as to why the Japanese have lower rates of prostate cancer.

Doerge D, Chang H. Inactivation of thyroid peroxidase by soy isoflavones in vitro and in vivo. *J Chromatogr B. Analyt Technolo Biomed Life Sci*, 2002, 777 (1-2), 269.

Drs. Doerge and Chang review the evidence in humans and animals for anti-thyroid effects of soy and its principal isoflavones, genistein and daidzein. They note that genistein interferes with estrogen receptors in rat prostate glands which " . . . may have implications for reproductive toxicity and carcinogenesis that warrant further investigation."

Lephart ED, Adlercreutz H, Lund TD. Dietary soy phytoestrogen effects on brain structure and aromatase in Long-Evans rats. *Neuroreport.* 2001, 16; 12, 16,:3451-3455.

"We found that dietary phytoestrogens: significantly decrease body and prostate weights, do not alter brain aromatase levels and significantly change during adulthood the structure of the sexually dimorphic brain region (i.e. anteroventral periventricular nucleus; AVPV) in male, but not in female rats. Since most commercial animal diets contain significant concentrations of phytoestrogens their influence on brain structure should be considered."

Spentzos D, Mantzoros C et al. Minimal effect of a low-fat/high soy diet for asymptomatic, hormonally naive prostate cancer patients. *Clin Cancer Res*. 2003 15, 9, 9, 3282-3287.

"PURPOSE: The effects of a low-fat diet or a low-fat diet with the addition of a soy supplement were investigated in a pilot Phase II study for asymptomatic, hormonally naive prostate cancer patients with rising prostate-specific antigen (PSA) levels. . . CONCLUSIONS: A low-fat diet with the subsequent addition of a soy supplement did

not result in a significant decline in PSA levels. The addition of soy protein had a modest effect on TTP. A potentially undesirable effect associated with the administration of soy was an increase in IGF-I serum levels."

Cohen LA, Zhao Z, Pittman B, Scimeca J. Effect of soy protein isolate and conjugated linoleic acid on the growth of Dunning R-3327-AT-1 rat prostate tumors. *Prostate.* 2003, 54, 3, 169-180.

"BACKGROUND: Epidemiologic and animal model studies suggest that consumption of soy isoflavones may be associated with reduced risk of prostate cancer (PC). In addition, animal model studies suggest that conjugated linoleic acid (CLA), a natural positional isomer of linoleic acid, inhibits tumor growth in various models, including models of PC. RESULTS: The results of this study indicate that neither an isoflavone-rich soy protein isolate (SPI), nor CLA inhibit the in vivo growth and development of prostate tumor cells when administered in the diet either singly or in combination. Moreover, at the highest concentrations SPI and CLA (i.e., 20% SPI, 1% CLA), there was a statistically significant increase in tumors volume over controls. Administration of SPI at 10% in the diet also enhanced tumor growth, whereas at 5%, SPI exerted no measurable effect. CLA administration alone had no observable effects on AT-1 tumor growth. . . CONCLUSION: These results, in an established rat model, suggest caution in using isoflavone-rich SPI in human studies involving advanced hormone-refractory prostate cancer until further investigation of these effects are completed. "

Probst-Hensch NM, Wang H et al. Determinants of circulating insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations in a cohort of Singapore men and women. *Cancer Epidemiol Biomarkers Prev.* 2003, 8, 739-746.

"Variation in the circulating concentrations of the insulin-like growth factor (IGF) system has been implicated in the etiology of chronic diseases including cancer (prostate, breast, colon, and lung), heart disease, type 2 diabetes, and osteoporosis. We searched for sociodemographic, anthropometric, reproductive, lifestyle, and dietary determinants of

IGF-I and insulin-like growth factor binding protein (IGFBP) -3 serum concentrations . . . Intake of soy was associated positively with IGF-I and molar ratio concentrations, but only in men. The results of this study lend additional support to the hypothesis that circulating IGF-I concentrations increase the risk of prostate, bladder, colorectal, and breast cancer."

Jenkins DJ, Kendall CW et al. Soy consumption and phytoestrogens: effect on serum prostate specific antigen when blood lipids and oxidized low-density lipoprotein are reduced in hyperlipidemic men. *J Urol.* 2003, 169, 2, 507-511.

"PURPOSE: Herbal remedies high in phytoestrogens have been shown to reduce serum prostate specific antigen (PSA) and have been proposed as a treatment for prostate cancer. Soy proteins used to lower serum cholesterol are rich sources of phytoestrogens. Therefore, we assessed the effect of soy consumption on serum PSA in men who had participated in cholesterol lowering studies. . . MATERIALS AND METHODS: For 3 to 4 weeks 46 healthy middle-aged men with a range of starting PSA values took soy (mean 44 gm. soy protein daily, 116 mg. isoflavones daily) or control foods, and a subgroup of men took a lower level of soy supplements for 3 months. PSA was measured at the start and end of each treatment. RESULTS: Soy had no significant effect on serum total or free PSA, independent of PSA starting value or isoflavone intake. . . "

Cohen LA, Zhao Z, Pittman B, Scimeca J. Effect of soy protein isolate and conjugated linoleic acid on the growth of Dunning R-3327-AT-1 rat prostate tumors. *Prostate.* 2003, 54, 3, 169-180.

"BACKGROUND: Epidemiologic and animal model studies suggest that consumption of soy isoflavones may be associated with reduced risk of prostate cancer (PC). In addition, animal model studies suggest that conjugated linoleic acid (CLA), a natural positional isomer of linoleic acid, inhibits tumor growth in various models, including models of PC. . . .RESULTS: The results of this study indicate that neither an isoflavone-rich soy protein isolate (SPI), nor CLA inhibit the in vivo growth and development of prostate tumor cells when administered in the diet either singly or in combination. Moreover, at the highest concentrations SPI and CLA (i.e., 20% SPI, 1%

CLA), there was a statistically significant increase in tumors volume over controls. Administration of SPI at 10% in the diet also enhanced tumor growth, whereas at 5%, SPI exerted no measurable effect. CLA administration alone had no observable effects on AT-1 tumor growth. CONCLUSION: These results, in an established rat model, suggest caution in using isoflavone-rich SPI in human studies involving advanced hormone-refractory prostate cancer until further investigation of these effects are completed."

Santti Developmental estrogenization and prostatic neoplasia. *Prostate*, 1994, 24, 2, 67-78.

"Evidence indicates that estrogen exposure during development may initiate cellular changes in the prostate which would require estrogens and/or androgens later in life for promotion of prostatic hyperplasia or neoplasia. . . The critical time for estrogen action would be during the development of prostatic tissue. We further suggest that estrogen-sensitive cells may remain in the prostate and be more responsive to estrogens alter in life or less responsive to the normal controlling mechanisms of prostate growth"

In other words, a male fetus exposed to soy phytoestrogens from his mother's diet would be more likely to develop prostate cancer later in life.

* * * * *

Pollard M, Wolter W, Sun L. Diet and the duration of testosterone-dependent prostate cancer in Lobund-Wistar rats. *Cancer Lett.* 2001, 173, 2, 127-131.

In its petition Solae sums this study up as follows: "Providing rats an ISP diet during age 12-24 months, the stage of spontaneous prostate tumor development, significantly reduces tumor incident compared with the controls on a soy meal diet."

The researchers, however, conclude their abstract with this revealing statement: "Dietary soymeal found in most natural ingredient diets may promote PC tumorigenesis, but only in L-W rats." L-W rats were developed, in the words of these researchers as "a unique model of spontaneous prostate cancer (PC)" that "shares many of its characteristics with the natural. history of PC in man, including (a) inherent predisposition, high production of testosterone and aging risk factors, (b) endogenous

tumorigenic mechanisms, and (c) early stage testosterone-dependent and late stage testosterone-independent tumors."

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Several studies suggest that if soy reduces rates of prostate cancer it might do so only for equol producers. If so, all males in the population would not stand to benefit from soy protein consumption. Also, green tea might be a factor in equol production.

Akaza H, Miyanaga N et al. Comparisons of percent equol producers between prostate cancer patients and controls: case-controlled studies of isoflavones in Japanese, Korean and American residents**.** *Jpn J Clin Oncol*. 2004, 34, 2, 86-89.

BACKGROUND: Our previous case-control study revealed that the Japanese residents in Japan could be divided into those who are able to degrade daidzein, a soybean isoflavone, to equol and those without this ability, and that the incidence of prostate cancer is higher in the latter group. . . CONCLUSIONS: These results suggest that the ability of producing equol or equol itself is closely related to the lower incidence of prostate cancer.

Miyanaga N, Akaza H et al. Higher consumption of green tea may enhance equol production. *Asian Pac J Cancer Prev*. 2003, 4, 4, 297-301

BACKGROUND: Our previous case-control study revealed that Japanese living in Japan and Koreans living in Korea can be divided into equol producers who have an ability to metabolize daidzein to equol and non-producers, and that the incidence of prostate cancer is higher in the latter group. In the present study, we examined relationships between type of food intake and the capacity for equol production in Japanese subjects. CONCLUSIONS: Our results suggest that higher consumption of soybean and green tea are strongly related to the establishment of a capacity for equol production.

Akaza H, Miyanaga N et al. Is daidzein non-metabolizer a high risk for

prostate cancer? A case-controlled study of serum soybean isoflavone concentration. *Jpn J Clin Oncol.* 2002, 32, 8, 296-300

"Equol itself or some unknown factor regulating the metabolism of daidzein is deeply involved in the biology of prostate cancer. Future studies are urgently needed to compare the incidence of daidzein metabolizers among various countries."

* * * * *

Finally, Solae has omitted discussion of the prevailing theories about why soy might be protective against the development of prostate cancer. Prostate cancer is generally thought to be dependent on exposure to male reproductive hormone. If soy confers protection, it is by altering endogenous hormone concentrations – by decreasing testosterone and androgen levels and estrogenizing men. While this might have valid pharmaceutical applications in cancer treatment, it seems inadvisable as a preventative treatment for the entire male population.

B.3.3. Gastro-Intestinal Cancer

In this section Solae states that a "thorough review of these studies reveals that consumption of soyfoods is related to a lower incidence of gastro-intestinal cancer in humans." To reach this conclusion, Solae had to omit numerous studies showing adverse effects.

The British Committee on Toxicology (COT) states that epidemiological studies exploring the relationship between soy consumption and the risk of stomach and colo-rectal cancer have "provided inconsistent results."
http://www.foodstandards.gov.uk/multimedia/webpage/phytoreportworddocs
Solae has found consistency, in part, because it purposely eliminated all studies pertaining to fermented soy products on the grounds that they are not as high in protein as

other soy foods. Increased rates of stomach and colorectal cancer have been found among people eating many fermented foods, including miso and other fermented soy products.

Solae has also incorporated all negative findings into its meta-analyses. This had the effect of obscuring the conclusions of **Nagata et al 2000,** an important study which showed that soy protein was associated with a lowered risk of stomach cancer but also with a higher risk of death from colorectal cancer. It hardly seems appropriate to claim benefit for a food that might prevent stomach cancer but put a person at higher risk for colon cancer.

Solae has also claimed benefits for soy protein based on studies in which the authors found their most significant associations with raw vegetables, green vegetables and allium-containing foods such as garlic and onions. We have summarized below important findings from several important studies pertaining dietary intake and gastrointestinal cancer. The studies by Gao, Ji, Lee, Hoshiyama, Shinchi, Takezaki, Nogoan and Ahn are studies in which the soy protein findings were exaggerated by Solae. Indeed, most provide excellent support for the FDA's health claim for fruits and vegetables preventing cancer, but cannot be used to support a health claim for soy protein.

Gao CM, Takezaki T et al. Protective effect of allium vegetables against both esophageal and stomach cancer: a simultaneous case-referent study of a high-epidemic area in Jiangsu Province, China. *Jpn J Cancer Res*. 1999 Jun;90(6):614-21.

To study the relation between allium vegetable intake and cancer of the esophagus (EC) and stomach (SC) in Yangzhong city, which is one of the highest-risk areas for these cancers in Jiangsu province, China . . . . The results showed that frequent intake of allium vegetables (including garlic, onion, Welsh onion and Chinese chives), raw vegetables, tomatoes and snap beans, and tea consumption were inversely associated with the risk for EC and SC. . .. The main results in the present study suggested that allium vegetables, like raw vegetables, may have an important protecting effect against not only stomach cancer, but also esophageal cancer.

Ji BT, Chow WH et al. Dietary habits and stomach cancer in Shanghai, China. *Int J Cancer*. 1998, 76, 5, 659-64.

". . . . Risks of stomach cancer were inversely associated with high consumption of several food groups, including fresh vegetables and fruits, poultry, eggs, plant oil, and some nutrients, such as protein, fat, fiber and antioxidant vitamins. By contrast, risks increased with increasing consumption of dietary carbohydrates. . . Similar increases in risk were associated with frequent intake of noodles and bread in both men . . . and women . . . In addition, elevated risks were associated with frequent consumption of preserved, salty or fried foods, and hot soup/porridge, and with irregular meals, speed eating and binge eating. . . . Our findings add to the evidence that diet plays a major role in stomach cancer risk and suggest the need for further evaluation of risks associated with carbohydrates and starchy foods as well as the mechanisms involved."

Lee JK, Park BJ et al. Dietary factors and stomach cancer: a case-control study in Korea. *Int J Epidemiol*. 1995, 24, 1, 33-41.

". . An increased risk of stomach cancer was noted among those with high consumption of stewed foods such as soybean paste stew and hot pepper-soybean stew, broiled fish, and those who liked salty food. However, mung bean pancake, tofu (soybean curd), cabbage, spinach, and sesame oil decreased the risk of stomach cancer. Stratified analysis by salt in combined foods, such as stewed foods and pickled vegetables, disclosed salt as being an important risk factor. . . " .

Takezaki T, Gao CM et al. Comparative study of lifestyles of residents in high and low risk areas for gastric cancer in Jiangsu Province, China; with special reference to allium vegetables. *J Epidemiol*. 1999, 9, 5, 297-305.

"There is a low risk area for gastric cancer in Jiangsu Province, China, where people frequently consume raw allium vegetables. The results of the survey suggest that frequent consumption of allium vegetables, in addition to other anticancer foods, may be a factor in low mortality for gastric cancer."

Ngoan LT, Mizoue T et al. .Dietary factors and stomach cancer mortality. *Br J Cancer*. 2002;87, 1, :37-42.

"The present study examined the relationship between stomach cancer and the low intake of fresh fruit and vegetables and/or a high intake of pickled, preserved or salted foods and frequent use of cooking oil. During 139,390 person-year of follow-up of over 13,000 subjects, 116 died from stomach cancer. . . . . controlling for age, sex, smoking and other dietary factors, a significant decline was found with a high consumption of green and yellow vegetables . . . . Reductions of between 40 and 50% were also observed with a high consumption of fresh foods (fruit, cuttle fish, tofu, and potatoes), but these associations were not statistically significant. The risk was significantly increased by the high consumption of processed meat . . "

Shinchi K, Ishii H et al. .Relationship of cigarette smoking, alcohol use, and dietary habits with Helicobacter pylori infection in Japanese men. Scand J Gastroenterol. 1997 32, 7, 651-655. .

". . . . Unexpectedly, the consumption of tofu (soybean curd) was significantly, negatively related to the infection . . . The seropositivity was unrelated to the consumption of pickled vegetables, soy paste soup, green tea, or garlic. . . The findings suggest that fresh vegetables may be protective against H. pylori infection. The study does not support either an increased risk of the infection associated with salty foods or a protective effect of green tea or garlic."

{H pylori is a major risk factor in stomach cancer]

Ahn YO. Diet and stomach cancer in Korea. *Int J Cancer*. 1997; Suppl 10, 7-9.

"An increased risk of stomach cancer was noted among people who frequently consume broiled meats and fishes, salted side dishes (salted/fermented fish products) and salty stewed foods, such as soybean paste thick stew. Frequent consumption of mung bean pancake, tofu, cabbage, spinach and sesame oil decreased the risk. In a recent cohort study in Seoul, green vegetables and soybean foods were associated with a decreased risk of stomach cancer. Case-control and cohort studies have reported that ginseng intake decreased the risk of gastric cancer."

Nomura AM, Hankin JH et al. Case-control study of diet and other risk factors for gastric cancer in Hawaii (United States). *Cancer Causes Control*. 2003, 14, 6, 547-558.

"The consumption of all vegetables, mainly dark green, light green, and yellow vegetables, reduced risk. Many of these vegetables contain beta-carotene, vitamin C, vitamin E or folate, which were also inversely related to gastric cancer risk. When these nutrients were analyzed simultaneously, the inverse association was mainly with beta-carotene. . . . These findings provide additional support that the consumption of dark green and yellow vegetables are protective against adenocarcinoma of the distal stomach."

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Hoshiyama Y, Sasaba T A case-control study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. *Cancer Causes Control.* 1992 3, 5, 441-448.

" . . . The consumption of raw vegetables was inversely related to the risk of stomach cancer, with a dose-response relation observed consistently in the comparisons with both sets of controls. In the multiple logistic regression, the consumption of raw vegetables showed a protective effect on stomach cancer while cigarette smoking had no

significant association, in both sets of controls.

Lee HH, Wu HY, et al. Epidemiologic characteristics and multiple risk factors of stomach cancer in Taiwan *Anticancer Res.* 1990, 10, 4, :875-81

"Comparison of the incidence of stomach cancer among Chinese in different countries showed a much lower incidence among Chinese in the USA than those in southeastern Asia. A hospital-based matched case-control study carried out in Taipei metropolitan areas showed a positive association of stomach cancer with blood type A, chronic gastric diseases, cigarette smoking, alcohol drinking, green tea drinking as well as consumption of salted meat, cured meat, smoked food, fried food and fermented beans.

There was also a significant negative association between the disease and the consumption of milk."

McKeown-Eyssen, GE, Bright-See E. Dietary factors in colon cancer: international relationships. *Nutr Cancer,* 1984, 6, 160-170.

This cross-cultural study of 38 countries found no association between soybean intake and risk of colon cancer.

Chyou PH, Nomura AM et al. A case-cohort study of diet and stomach cancer. *Cancer Res.* 1990, 50, 23, 7501-7504.

". . . We found that the consumption of all types of vegetables was protective against stomach cancer.. . . Similar but weaker protective effects from consumption of green and cruciferous vegetables were also observed. In addition, an inverse association between stomach cancer risk and intake of fruits was noted . . . but this inverse trend was weakened after the effect of cigarette smoking was taken into account. There were no other dietary factors significantly associated with the risk of gastric cancer

You WC, Blot WJ et al. Diet and high risk of stomach cancer in Shandong, China. *Cancer Res.* 1988; 48, 12, 3518-23.

". . . A case-control investigation involving interviews with 564 stomach cancer patients and 1131 population-based controls was conducted to evaluate reasons for the exceptionally high rates of stomach cancer in Linqu, a rural county in Shandong Province in northeast China. Daily consumption of sour pancakes, a fermented indigenous staple, was associated with a 30% increase in risk. . . . risks tended to decrease in proportion to increasing consumption of fresh vegetables and fruits. This protective effect was more pronounced for vegetables, with those in the highest quartile of intake at less than one-half the risk of those in the lowest. Stomach cancer risks also declined with increasing dietary intake of carotene, vitamin C, and calcium, but not retinol. "

Galanis DJ, Kolonel LN et al. Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. *Int J Epidemiol*. 1998, 27, 2, 173-180

". .. . The combined intake of fresh fruit and raw vegetables was inversely associated with the risk of gastric cancer in the total cohort, and among the men no significant relationships were found between gastric cancer incidence and the intake of pickled vegetables, miso soup, dried or salted fish, or processed meats among either gender. . ."

Hu JF, Lin YY et al. Diet and cancer of the colon and rectum: a case-control study in China. *Int J Epidemiol*, 1991, 20, 362-367.

. . . Vegetables, particularly green vegetables, chives and celery, have a strong protective effect against colorectal cancer. Reduced consumption of meat, eggs, bean products and grain was associated with increasing risk for cancer of the rectum. Alcohol intake was found to be an important risk factor for developing colon cancer and male rectal cancer. . . "

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Solae omitted several key studies that link soy protein to the development of intestinal cancers or that document precancerous damage caused by soy protein.

McIntosh GH, Regester GO et al. Dairy proteins protect against dimetylhydrazine-induced intestinal cancers in rats. *J Nutr*, 1995, 125, 809-816.

" . . . The tumor data indicated that dietary whey protein and casein were more protective against the development of intestinal cancers in rats than were the red meat and soybean diets. No statistically significant difference was observed between the effects of casein and the effects of whey protein In addition, no significant difference in tumor

incidence or burden could be measured between the animals fed the red meat diet and those fed the soybean protein diet. . . . Our data also suggest that, like meat, soybean may not be an optimal source of protein for the gastrointestinal tract,

Govers MJ, Lapre JA et al. Dietary soybean protein compared with casein damages colonic epithelium and stimulates colonic epithelial proliferation in rats. *J Nutr* 1993, 123, 1709-1713.

". . . epithelial cell damage and proliferation of colonic epithelium (measured as in vivo incorporation of tritiated thymidine into DNA) were greater in rats fed soybean protein. The stimulation of colonic proliferation by soybean protein is consistent with the observed increase in luminal cytolytic activity and epithelial cell damage. We conclude that the stimulatory effect of soybean protein on endogenous magnesium excretion is due to a soybean protein-specific damage of colonic epithelial cells, which results in a compensatory epithelial cell hyperproliferation. "

{Cell proliferation has been identified as an early biomarker of colon cancer risk.}

Davies MJ, Bowey EA et al. Effects of soy or rye supplementation of high-fat diets on colon tumour develop in azoxymethane-treated rats. *Carcinogenesis*, 1999, 20,

927-931.

". . . Demonstrated that soy (250 mg isoflavones/kg diet) did not protect against experimentally induced colon cancer in rats. Indeed those given isoflavones had increased numbers of small ACF, thought to be markers for the disease, at 12 weeks. However a diet containing 30% rye bran significantly reduced the number of colon tumors. Although there was no change in the total number of ACF at 12 weeks, with the

rye diet, the total number of large ACF was reduced. . . These results suggest that soy isoflavones have no effect on the frequency of colonic tumours in this model while rye bran supplementation decreases the frequency of colon cancer. This effect is due not to a decrease in early lesions but in their progression to larger multi-crypt ACF. The study also supports the hypothesis that larger ACF are more predictive of subsequent tumorigenicity."

Soybeans also contain antinutrients known as lectins that bind to the villi and crypt cells of the small intestine. Lectin binding contributes to cell death, a shortening of the villi, a diminished capacity for digestion and absorption, cell proliferation in the crypt cells, interference with hormone and growth factor signaling and unfavorable population shifts among the microbial flora. All these factors contribute towards intestinal cancers.

The following studies are relevant:

Jindal S, Soni GL, Singh R. Biochemical and histopathological studies in albino rats fed on soyabean lectin. *Nutr Rep Inter*, 1984, 29, 95-106.

Torres-Pinedo R. Lectins and the intestine. *J Pediatr Gastroenterol Nutr*, 1983, 2, 588-594.

Ament ME, Rubin CE. Soy protein – another cause of the flat intestinal lesion. *Gastroenterol*, 1972, 62, 2, 227-234.

Poley JR, Klein AW. Scanning electron microsocopy of soy protein-induced damage of small bowel mucosa in infants. *J. Pediatr Gastroenterol Nutr,* 1983, 2, 2, 271-287

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Finally, Solae claims that soy protein is a high-quality, complete protein, containing all the essential amino acids. The sulfur containing amino acid methionine, however, is so underrepresented in soy protein that it must be added to soy infant formula and to soy-based animal feeds. This deficiency makes soy protein a questionable food

for colon cancer prevention. As the following studies indicate, methionine has been shown to be prevent colon cancer.

Fuchs CS, Willett WC et al. The influence of folate and multivitamin use on the familial risk of colon cancer in women. *Cancer Epidemiol Biomarkers Prev*. 2002 Mar;11(3):227-34.

Low intake of folate and methionine and heavy alcohol consumption have been associated with an increased overall risk of colon cancer, possibly related to their role in methylation pathways. . . . Our results suggest that higher intake of folate and methionine, regular use of multivitamins containing folate, and avoidance of moderate to heavy alcohol consumption may diminish the excess risk of colon cancer associated with a family history of the disease.

Giovannucci E, Stampfer MJ et al. ,Folate, methionine, and alcohol intake and risk of colorectal adenoma. *J Nutr*. 1993 Oct;123(10):1709-13J.

" . . . The apparent protective effect of fresh fruits and vegetables, the major folate sources, on colorectal cancer incidence suggests that a methyl-deficient diet contributes to occurrence of this malignancy. Low dietary folate and methionine and high intake of alcohol may reduce levels of S-adenosylmethionine, which is required for DNA methylation. . .CONCLUSIONS: Folate, alcohol, and methionine could influence methyl group availability, and a methyl-deficient diet may be linked to early stages of colorectal neoplasia. A dietary pattern that increases methyl availability could reduce incidence of colorectal cancer. . . "

APPENDIX III: SCIENTIFIC EVIDENCE – OTHER CANCERS

Solae provides summaries of a number of studies that "reflect a trend that consumption of soyfoods is related to a lower risk of cancerous diseases. However, the number of studies is limited and findings are not consistent in certain types of cancers."

We would agree that the studies are inconsistent and sometimes contradictory. However,we do not agree that the number of studies is limited; in fact, there are a large number of studies related to thyroid and pancreatic cancers as well as two studies that implicate soy in the development of childhood leukemia.

The American Cancer Society reports that overall thyroid cancer incidence across all ages and races is now increasing at 1.4 percent per year and that incidences rose 42.1 percent between 1975 and 1996, with the largest increases among women. Thyroid carcinoma is one of the most common cancers among US children and adolescents, with approximately 75 percent occurring to adolescents between the ages of 15 and 19. The National Cancer Institute (NCI) comments that "the preponderance of thyroid cancer in females suggest that hormonal factors may mediate disease occurrence." "Hormonal factors" could include the phytoestrogens in soy protein products.

There is also substantial body of evidence proving that the antinutrients known as protease inhibitors (or trypsin inhibitors) in soy causes pancreatic hyperplasia, a precursor to pancreatic cancer. It may not be coincidental that pancreatic cancer recently moved up to fourth place as a cause of cancer deaths in men and women in the United States as consumption of soyfoods in this country has increased. In the 1970s and 1980s, several researchers studying protease-inhibitor damage on the pancreas noted that pancreatic cancer had then moved up to fifth place and wondered whether there might be a soybean-protease inhibitor connection. The fact that this ongoing rise has occurred along with a rise in the human consumption of soybeans does not prove cause and effect. However, looking at the increase in pancreatic cancer cases alongside pertinent animal studies is suggestive -- and sobering. No one appreciates the safety issues better than Irvin E. Liener, Ph.D, a leading

expert on plant toxins and antinutrients. In 1998, he warned that “Soybean trypsin inhibitors do in fact pose a potential risk to humans when soy protein is incorporated into the diet." (Liener IE. Letter to Dockets Management Branch, Food and Drug Administration, December 31, 1998).

Finally, Solae fails to open a discussion about soy protein’s link to immune system suppression, a possibility that further undermines any assertion that soy protein affords protection against cancer.

The following studies support our position that the claim that soy protein prevents cancer cannot be justified.

Divi RL, Chang HC, Doerge DR. Anti-thyroid isoflavones from soybean: isolation, characterization, and mechanisms of action. *Biochem Pharmacol*. 1997. 10, 1087-96.

”The soybean has been implicated in diet-induced goiter by many studies. The extensive consumption of soy products in infant formulas and in vegetarian diets makes it essential to define the goitrogenic potential. In this report, it was observed that an acidic methanolic extract of soybeans contains compounds that inhibit thyroid peroxidase-(TPO) catalyzed reactions essential to thyroid hormone synthesis. . . . Because inhibition of thyroid hormone synthesis can induce goiter and thyroid neoplasia in rodents, delineation of anti-thyroid mechanisms for soy isoflavones may be important for extrapolating goitrogenic hazards identified in chronic rodent bioassays to humans consuming soy products.”

Divi RL, Doerge DR Inhibition of thyroid peroxidase by dietary flavonoids. *Chem Res Toxicol*. 1996, 9, 1, 16-23.

“Flavonoids are widely distributed in plant-derived foods and possess a variety of biological activities including antithyroid effects in experimental animals and humans. . . . These inhibitory mechanisms for flavonoids are consistent with the antithyroid effects

observed in experimental animals and, further, predict differences in hazards for antithyroid effects in humans consuming dietary flavonoids. In vivo, suicide substrate inhibition, which could be reversed only by de novo protein synthesis, would be long-lasting. However, the effects of reversible binding inhibitors and alternate substrates would be temporary due to attenuation by metabolism and excretion. The central role of hormonal regulation in growth and proliferation of thyroid tissue suggests that chronic consumption of flavonoids, especially suicide substrates, could play a role in the etiology of thyroid cancer."

Sheehan DM. Herbal medicines, phytoestrogens and toxicity: risk:benefit considerations. *Proc Soc Exp Biol Med.* 1998, 217, 3, 379-85.

"There are several suggested health benefits of phytoestrogens, particularly those found in soy products. Herbal medicines are also widely thought to confer health benefits. Additionally, drugs are prescribed to improve human health, but unlike phytoestrogens and herbal medicines, toxicities are defined in experimental animals and monitored in humans before and after marketing. Knowledge of toxicity is crucial to decrease the risk:benefit ratio; this knowledge defines appropriate conditions for use and strategies for development of safer products. However, our awareness of the toxicity of herbal medicines and phytoestrogen-containing foods is dramatically limited compared to drugs. Some aspects of the toxicity of herbal medicines are briefly reviewed; it is concluded that virtually all of our knowledge is derived from human exposures leading to acute toxicities. Importantly, detection of toxicity is sporadic, and little information is available from prior animal experimentation. Additionally, well-organized monitoring of human populations (as occurs for drugs) is virtually nonexistent. Important toxicities with long latencies are particularly difficult to associate with a causative agent during or even after large scale exposures, as exemplified by tobacco smoking and lung cancer; estrogen replacement therapy and endometrial cancer; diethylstilbestrol and reproductive tract cancers; and fetal alcohol exposure and birth defects. These considerations suggest that much closer study in experimental animals and human populations exposed to

phytoestrogen-containing products, and particularly soy-based foods, is necessary. Among human exposures, infant soy formula exposure appears to provide the highest of all phytoestrogen doses, and this occurs during development, often the most sensitive life-stage for induction of toxicity. Large, carefully controlled studies in this exposed infant population are a high priority."

Newbold RR, Banks EP et al. Uterine adenocarcinoma in mice treated neonatally with genistein. *Cancer Res.* 2001 Jun 1;61(11):4325-8.

"The developing fetus is uniquely sensitive to perturbation with estrogenic chemicals. The carcinogenic effect of prenatal exposure to diethylstilbestrol (DES) is the classic example. Because phytoestrogen use in nutritional and pharmaceutical applications for infants and children is increasing, we investigated the carcinogenic potential of genistein, a naturally occurring plant estrogen in soy, in an experimental animal model previously reported to result in a high incidence of uterine adenocarcinoma after neonatal DES exposure. Outbred female CD-1 mice were treated on days 1-5 with equivalent estrogenic doses of DES (0.001 mg/kg/day) or genistein (50 mg/kg/day). At 18 months, the incidence of uterine adenocarcinoma was 35% for genistein and 31% for DES. These data suggest that genistein is carcinogenic if exposure occurs during critical periods of differentiation. Thus, the use of soy-based infant formulas in the absence of medical necessity and the marketing of soy products designed to appeal to children should be closely examined."

Doerge DR, Sheehan DM. Goitrogenic and estrogenic activity of soy isoflavones. *Environ Health Perspect*, 2002, 110, suppl 3, 349-353.

"Soy is known to produce estrogenic isoflavones. Here we briefly review the evidence for binding of isoflavones to the estrogen receptor, in vivo estrogenicity and developmental toxicity, and estrogen developmental carcinogenesis in rats. . . Although safety testing of natural products, including soy products, is not required, the possibility that widely consumed soy products may cause harm in the human population via either or both estrogenic and goitrogenic activities is of concern."

Whitten PL, Lewis C et al. Potential Adverse Effects of phytoestrogens. *J Nutr,* 1995, 125, 771S-776S.

"Evaluation of the potential benefits and risks offered by naturally occurring plant estrogens requires investigation of their potency and sites of action when consumed at natural dietary concentrations. . . . . These findings illustrate the broad range of actions of these natural estrogens and the variability in potency across endpoints. This variability argues for the importance of fully characterizing each phytoestrogen in terms of its sites of action, balance of agonistic and antagonistic properties, natural potency, and short-term and long-term effects."

` **Strauss L, Santti R et al.** Dietary phytoestrogens and their role in hormonally dependent disease. *Toxicol Lett,* 1998, 28, 102-103, 349-354.

"Epidemiological studies suggest that diets rich in phytoestrogens (plant estrogens), particularly soy and unrefined grain products, may be associated with low risk of breast and prostate cancer. It has also been proposed that dietary phytoestrogens could play a role in the prevention of other estrogen-related conditions, namely cardiovascular disease, menopausal symptoms and post-menopausal osteoporosis. However, there is no direct evidence for the beneficial effects of phytoestrogens in humans. All information is based on consumption of phytoestrogen-rich diets, and the causal relationship and the mechanisms of phytoestrogen action in humans still remain to be demonstrated. In addition, the possible adverse effects of phytoestrogens have not been evaluated. It is plausible that phytoestrogens, as any exogenous hormonally active agent, might also cause adverse effects in the endocrine system, i.e. act as endocrine disrupters."

Whitten PL, Patisaul HB. Cross-species and interassay comparisons of phytoestrogen actions. *Envir Health Perspect*, 2001, 109, Suppl 1, 5-20.

"In vivo data show that phytoestrogens hav ea wide range of biologic effects doses and plasma concentrations seen with normal human diets. Signfiicant in vivo resonses have been observed in animal and human tests for bone, breast, ovary, pituitary, vasculature, prostate and serum lipis. . Steroidogenesis and hypothalmamic-pituitary-

gonadal axis appear to be important loci of phytoestrogen actions, but these inferences must be tentative because good dose-response data are not available for many end-points."

Anderson D, Dobrzynska MM, Basaran N. Effect of various genotoxins and reproductive toxins in human lymphocytes and sperm in the Comet assay. *Teratog Carcinog Mutagen*. 1997;17(1):29-43.

"There have been conflicting reports as to whether the mean sperm count in some men has diminished over the last 50 years. The downward trend has been suggested to coincide with an increase in exposure to estrogen-like compounds. These estrogenic substances are ubiquitous in the environment. We have examined the effect of such substances (diethylstilbestrol, beta-estradiol, daidzein, genestein, and nonylphenyl) in the single cell gel electrophoresis assay (Comet assay) in human sperm and compared responses with those from human peripheral lymphocytes in the same donor and in peripheral lymphocytes from a female donor. In addition, effects from the estrogens have been compared to those from known reprotoxins and genotoxins. These include lead sulfate, nitrate and acetate, dibromochloropropane, ethylene glycol monoethyl ether, 1,2-epoxybutene, and 1,2,3,4-diepoxybutane. All compounds produced positive responses, but ethylene glycol monoethyl ether only produced positive responses in sperm cells in the male and not in peripheral lymphocytes, and similarly the phytoestrogens (genistein, daidzein) were less responsive in the peripheral lymphocytes in the male than in the sperm. This may be due to greater sensitivity of sperm cells because of their lack of repair. However, since damage was generally seen over a similar dose range, a one-to-one ratio of somatic and germ cell damage was observed and has implications for man for risk assessment purposes."

Yellayi S, Naaz A et al. The phytoestrogen genistein induces thymic and immune changes: a human health concern? *Proc Natl Acad Sci* U S A. 2002 99, 11, 7616-7621.

"Use of soy-based infant formulas and soy/isoflavone supplements has aroused

concern because of potential estrogenic effects of the soy isoflavones genistein and daidzein. Here we show that s.c. genistein injections in ovariectomized adult mice produced dose-responsive decreases in thymic weight of up to 80%. Genistein's thymic effects occurred through both estrogen receptor (ER) and non-ER-mediated mechanisms, as the genistein effects on thymus were only partially blocked by the ER antagonist ICI 182,780. Genistein decreased thymocyte numbers up to 86% and doubled apoptosis, indicating that the mechanism of the genistein effect on loss of thymocytes is caused in part by increased apoptosis. Genistein injection caused decreases in relative percentages of thymic CD4(+)CD8(-) and double-positive CD4(+)CD8(+) thymocytes, providing evidence that genistein may affect early thymocyte maturation and the maturation of the CD4(+)CD8(-) helper T cell lineage. Decreases in the relative percentages of CD4(+)CD8(-) thymocytes were accompanied by decreases in relative percentages of splenic CD4(+)CD8(-) cells and a systemic lymphocytopenia. In addition, genistein produced suppression of humoral immunity. Genistein injected at 8 mg/kg per day produced serum genistein levels comparable to those reported in soy-fed human infants, and this dose caused significant thymic and immune changes in mice. Critically, dietary genistein at concentrations that produced serum genistein levels substantially less than those in soy-fed infants produced marked thymic atrophy. These results raise the possibility that serum genistein concentrations found in soy-fed infants may be capable of producing thymic and immune abnormalities, as suggested by previous reports of immune impairments in soy-fed human infants."

The following studies offer a good cross section of the evidence that soy protein stresses the pancreas and may contribute to or cause cancer.

Rackis JJ, Gumbmann MR, Liener IE. The USDA Trypsin Inhibitor Study,I. Background, objectives and procedural details. *Qual Plant Foods Hum Nutr,* 1985, 35, 213-242.

Liener IE, Nitsan Z et al. The USDA Trypsin inhibitor study, II. Timed release biochemical changes in the pancreas of rats. *Qual Plant Foods Hum Nutr*, 1985, 35, 243-257.

Spangler WL, Gumbmann MR et al. The USDA Trypsin Inhibitor Study, III. Sequential development of pancreatic pathology in rats. *Qual Plant Foods Hum Nutr*, 1985, 35, 359-274.

Gumbmann MR, Spangler WI et al. The USDA Trypsin Inhibitor Study, IV. The chronic effects of soy flour and soy protein isolate on the pancreas in rats after two years. *Qual Plant Foods Hum Nutr*, 1985, 35, 275-314.

Roebuck BD. Trypsin Inhibitors: potential concern for humans? *J. Nutr*, 1987, 117, 398-400.

Myers BA, Hathcock J et al. Effects of dietary soya bean trypsin inhibitor concentrate on initiation and growth of putative preneoplastic lesions in the pancreas of the rat. *Food Chem Toxic*, 1991, 29, 7, 437-443.

Liener IE. Letter to the editor: Soybean protease inhibitors and pancreatic carcinogenesis, *J. Nutr*, 1996, 126, 582-583.

Studies implicating soy and leukemia are as follows:

Strick R, Strissel PL et al. Dietary bioflavonoids induce cleavage in the MLL gene and may contribute to infant leukemia. *Proc Natl Acad Sci* USA, 2000, 25, 97, 9, 4790-4795.

”Chromosomal translocations involving the MLL gene occur in about 80% of infant leukemia. In the search for possible agents inducing infant leukemia, we identified bioflavonoids, natural substances in food as well as in dietary supplements, that cause site-specific DNA cleavage in the MLL breakpoint cluster region (BCR) in vivo. The MLL BCR DNA cleavage was shown in primary progenitor hematopoietic cells from healthy newborns and adults as well as in cell lines; it colocalized with the MLL BCR cleavage site induced by chemotherapeutic agents, such as etoposide (VP16) and doxorubicin (Dox). Both in vivo and additional in vitro experiments demonstrated

topoisomerase II (topo II) as the target of bioflavonoids similar to VP16 and Dox. Based on 20 bioflavonoids tested, we identified a common structure essential for topo II-induced DNA cleavage. Reversibility experiments demonstrated a religation of the bioflavonoid as well as the VP16-induced MLL cleavage site. Our observations support a two-stage model of cellular processing of topo II inhibitors: The first and reversible stage of topo II-induced DNA cleavage results in DNA repair, but also rarely in chromosome translocations; whereas the second, nonreversible stage leads to cell death because of an accumulation of DNA damage. These results suggest that maternal ingestion of bioflavonoids may induce MLL breaks and potentially translocations in utero leading to infant and early childhood leukemia."

Editorial -- Infantile Leuemia and soybeans – a hypothesis *Leukemia*, 1999, 13, 317-320.

"Recent molecular-genetic studies have revealed that in the majority of patients with secondary leukemia induced by topoisomerase II (topo II) inhibitors and also with infantile acute leukemia (IAL), the breakpoints are clustered within scaffold attachment regions (SARS) of 3"-MLL-bcr near exon 9. Genistein, abundant in soybeans, is reported to be a potent nonintercalative topo II inhibitor. It interferes with the break-reseal reaction of topo II by stabilizing a cleavable complex, which in the presence of detergents, results in DNA strand breaks. The present study revealed that genistein induced chromatid-type aberrations in which chromatid exchanges are often observed. Genistein seems to act in a manner very similar to that of VP-16, although the latter is reported to produce both chromatid-and-chromosome-type aberrations. In view of this pharmacological similarity between genistein and VP-16, and also the similarity of breakpoint clustering regions within the MLL gene in reported cases with secondary leukemia and IAL, genistein may be largely responsible for the development of IAL."

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IN CONCLUSION: We have provided abundant scientific evidence indicating that consumption of soy protein/soy isoflavones can contribute to various types of cancer. Allowance of a claim that soy prevents cancer would be false and misleading and would constitute a betrayal of public trust.